PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK2004/000844	03.12.2004	03.12.2004

International Patent Classification (IPC) or both national classification and IPC
A61K9/14, A61K9/16, A61K47/02, A61K31/58

Applicant
LIFECYCLE PHARMA A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Scarponi, U

Telephone No. +31 70 340-3292

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/DK2004/000844

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/DK2004/000844

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	16-22,24-28,32-35,42
	No:	Claims	1-15,23,29-31,36-41,43-57
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-57
Industrial applicability (IA)	Yes:	Claims	1-57
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/DK2004/000844

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: US 2003083309 A1 (C.M. ADEYEYE ET AL.) 1 May 2003 (2003-05-01)
D2: WO 9939700 A (VECTORPHARMA S.P.A., TRIESTE, IT) 12 August 1999 (1999-08-12)
D3: WO 9600567 A (EASTMAN KODAK) 11 January 1996 (1996-01-11)
D4: US 5302401 A (G.G. LIVERSIDGE ET AL.) 12 April 1994 (1994-04-12)
D5: WO 03082247 A (TEVA) 09 October 2003 (2003-10-09)
D6: DATABASE CA, ACCESSION NUMBER 122:17243
& JP06256193 (TOKYO TANABE CO.,JP) 13 September 1994 (1994-09-13)
D7: DATABASE CA, ACCESSION NUMBER 114:214473
& JP02282330 (TOKYO TANABE CO.,JP) 19 November 1990 (1990-11-19)

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

V.1. Present **claims 8,9,16-20,22,24-28,32-33,36,40-41,55-56** do not meet the requirements of **Article 6 PCT** in that the matter for which protection is sought is not clearly defined. The following statements used in said **claims 8,9,16-20,22,24-28,32-33,36,40-41,55-56** are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (**Article 6 PCT**): ***"... a similar commercially available danazol-containing product...", "... tested in an in-vitro dissolution test ... employing a dissolution medium comprising a buffer...", "... tested in an in-vitro dissolution test employing a dissolution medium having a ph ...", "... silica acid or a derivative thereof ...", "... an oily material...", "... a material suitable for forming solid dispersions...", "... the group consisting of cellulose derivatives including ...PVP and PVA ...".***

Furthermore it is clear both from the description on pages 18-21, from the present Examples and especially from **present claim 41** that the following technical features are **essential to the definition of the invention** in order to achieve the desired technical effect:

(1) the oily material mentioned in **present independent claim 36** should be in fact a material

chosen from the materials described in the description on page 18, line 9 up to page 21, line 7;
(2) the material suitable for forming solid dispersions mentioned in **present claim 40** should be in fact a material chosen from the materials mentioned in **present claim 41 and especially the materials employed in the present examples.**
Since present independent **claims 36, 40** do not contain these features, they do not meet the requirement following from **Article 6 PCT** taken in combination with **Rule 6.3 b) PCT** that any independent claim must contain all the technical features essential to the definition of the invention.

V.2. Above all, it must be here especially stressed the fact that **present independent claims 1,4-6,8,11-13,23,51** do not meet the requirements of **Article 6 PCT taken in combination with Rule 6.3 PCT**, because the claims are not clear, insofar as they are formulated by attempting to define the subject-matter of the invention, or a feature thereof, in terms of the result(s) to be achieved (***"...wherein the composition upon oral administration to a mammal in need thereof releases the active substance in a controlled manner and exhibits an AUC/AUCcontrol value ...", "...and exhibits a W50 that is about ...", "...and exhibits a Cdiff of...", "...and does not exhibits a significant adverse food effect as evidenced by ...", "... the composition being essentially bioequivalent with ...", "... the composition ...reduces gastrointestinal side-effects...provides an equivalent therapeutic effect...", "... the composition ...reduces inter- and/or intra-individual variations...", "...wherein the composition upon oral administration to a mammal in need thereof has a delayed release of the active substance ...", "...wherein the solid dosage form upon oral administration to a mammal in need thereof exhibits an AUC/AUCcontrol value ..."***).
They only amount to an undue reiteration of the underlying technical problem, thereby resulting in lack of clarity and conciseness. The subject-matter for which protection is desidered should be defined in concrete terms, i.e. in terms of **how** the aforementioned result is to be achieved and in terms clearly defining the instructions enabling the person skilled in the art to reproduce in practice the invention **without undue burden and without inventive skills** . This does not seem to be the case of **present claims 1,4-6,8,11-13,23,51** insofar as they make **uniquely** reference to **"in vivo"** tests and effects. It must be here specifically pointed out that "in vivo" tests (particularly when stated to be performed indifferently on a human or animal patient!) are subject to a great individual variability and therefore do not clearly define the subject matter of the claims.

More particularly and specifically, it must be here pointed out that the claimed **"in vivo"** properties and effects of the claimed compositions and dosage forms cannot serve to clearly distinguish the claimed product as they are not correlate to the constitution of product itself, said constitution being defined - on the other hand - as merely consisting of the active agent and an excipient (chosen among a large and generic variety of excipients and additives). Very likely, many combinations of danazol and an excipient could show the described and claimed **"in vivo"** properties and effects .

V.3. Furthermore, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-15,23,30-31,44-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D1**, and therefore the criteria of **Article 33(1) PCT** are not met.
In fact the document D1 discloses controlled release solid peroral or buccal dosage forms (e.g. tablets) comprised of danazol in a polymer matrix, said forms showing favourable dissolution properties and especially bioavailability properties in comparison with previously available commercial products (notably Danocrine^{R}), as it is shown by relative AUC values.
Analogously, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-15,23,30-31,36-38,43-46,48-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D2**, and therefore the criteria of **Article 33(1) PCT** are not met.
In fact the document D2 discloses nanoparticulate compsns. for the oral administration of liposoluble/poorly soluble drugs (e.g. DANAZOL) comprising a LIPIDIC/OILY SUBSTANCE endowed with improved bioavailability (e.g. better AUC) in comparison with the prior art products.
In the same way, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-9,11-12,30-31,36-38,43-45,48-49,51-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D3**, and therefore the criteria of **Article 33(1) PCT** are not met.
In fact the document D3 discloses danazol nanoparticulate compsns. wherein particles are surface-modified by adsorption of alkylene oxides copolymers.
Analogously, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-9,11-12,30-31,43-45,48-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D4**, and therefore the criteria of **Article 33(1) PCT** are not met.
In fact the document D4 discloses compositions comprising lyophilisates comprised of DANAZOL SURFACE-MODIFIED NANOPARTICLES and CRYOPROTECTANTS.

Analogously, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-9,11-12,29-31,39-41,43-49,51-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D5**, and therefore the criteria of **Article 33(1) PCT** are not met.

In fact the document D5 discloses oral compsns. comprised of drug (e.g. DANAZOL) microparticles on a carrier (non-pareil) particles, further compressed to tablets. MICROPARTICLES ARE OBTAINED FROM SOLID SOLUTIONS OF THE DRUG IN A SUBLIMABLE CARRIER.

Analogously, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-15,23,30-31,36-37,43-46,48-49,51-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D6**, and therefore the criteria of **Article 33(1) PCT** are not met.

In fact the document D6 discloses sustained-release oral compsns. comprised of danazol (coated) granules showing **AUC data comparable with data reported in the present example 4d for the inventive compositions.**

Finally, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-9,11-15,23,30-31,36-38,43-46,48-49,51-57** is not new in the sense of **Article 33(2) PCT** in the light of the **document D7**, and therefore the criteria of **Article 33(1) PCT** are not met.

In fact the document D7 discloses sustained-release oral compsns. comprised of danazol compsns. comprised of danazol surface-modified microcrystals on a cellulose derivative or saccharide carrier and **showing specified favourable dissolution properties in 0.1 N HCl (i.e. at pH 1).**

In conclusion, the above-mentioned lack of clarity notwithstanding, the subject-matter of **present claims 1-15,23,29-31,36-41,43-57** is not new in the sense of **Article 33(2) PCT** in the light of all the **documents D1 to D7**, and therefore the criteria of **Article 33(1) PCT** are not met.

V.3. Furthermore, the subject matter of **present claims 1-57** does not involve an inventive step in the sense of **Article 33 (3) PCT** , and therefore the requirements of **Article 33 (1) PCT** are not met.

In fact the **documents D1-D7** mentioned above in paragraph **V.2.** all appear to be of particular relevance as far as the inventive step is concerned (**Article 33 (3) PCT**).

These documents do not only solve indeed the **same problem** as defined in the present

Application, namely the preparation of particulate danazol compositions endowed with specified bioavailability and dissolution properties, but they teach also the **same solution**, namely to compound the active agent with a suitable array of excipients or to dissolve it in a suitable array of excipients in the form of a solid solution, in order to get a particulate material to be further processed to suitable solid dosage forms.

Therefore - **as far as novel subject matter is concerned** - the present Application does not seem to fulfill the requirements of **Art. 33 (3) PCT** over these prior art documents, unless an **unexpected effect** for the present composition(s) (**as far as novel**) over the prior art compositions can be demonstrated.